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Antiprotozoal Agents

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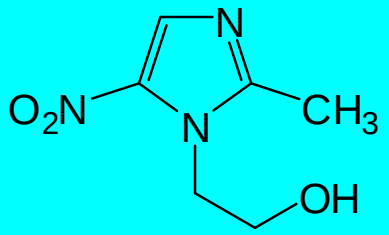
A- Antiamoebic Drugs

- **Amebiasis is caused by *Entamoeba histolytica* that invade the wall of the colon (intestinal) or other parts of the body e.g., liver, lung, skin (extraintestinal).**

- **Amebicides are either**
  - **Direct amebicides (used for amebic dysentery, intestinal)**
  - **Systemic amebicides (used for extraintestinal infections)**
  - **Mixed amebicides (used for both cases).**

1) 5-Nitroimidazoles

Metronidazole



2-Methyl-5-nitroimidazole-1-ethanol

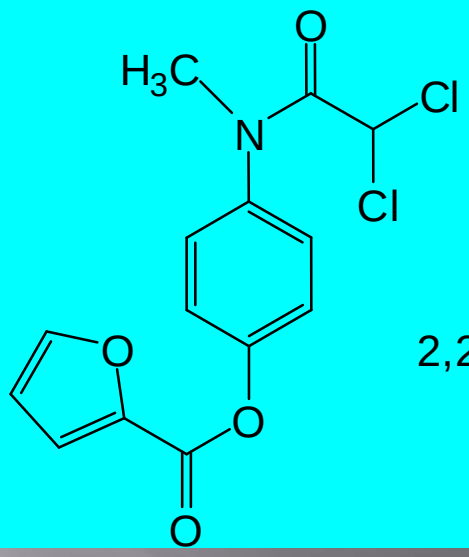
Tinidazole

1-(2-(ethylsulfonyl)ethyl)-2-methyl-5-nitro-1*H*-imidazole

- **Metronidazole and Tinidazole are effective against both intestinal and hepatic amebiasis.**
- **Metronidazole is effective against gram-negative anaerobes such as *Bacteroids* and *Fusobacterium* species, and gram-positive anaerobic bacilli and cocci.**
- **Metronidazole is metabolized to oxidized or conjugated forms. The 2-hydroxy metabolite is active (CH_3→ CH_2OH).**
- **The 5-nitro group reduced by the organism into reactive intermediates such as nitroso, hydroxylamine and amino that covalently bind to the DNA of the organism triggering the lethal effect NO_2→NO→NH_2).**

2) Diloxanide

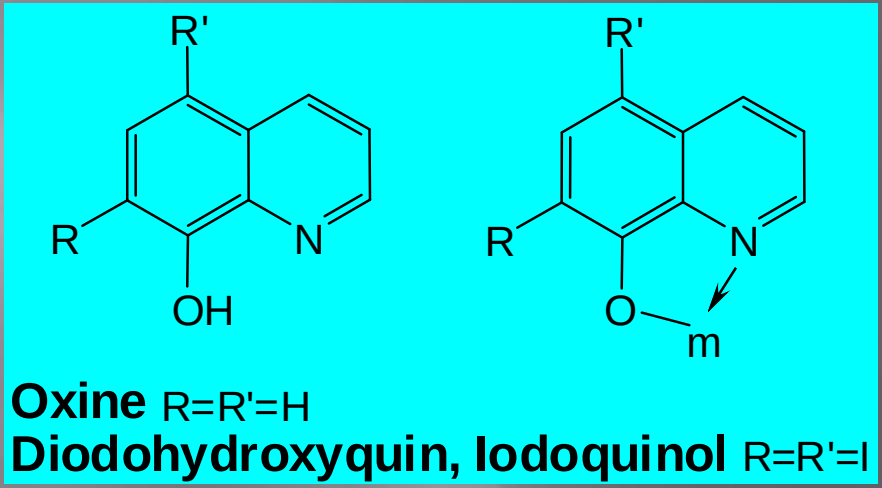
Diloxanide furoate



2,2-Dichloro-4'-hydroxy-N-methylacetanilide-2'-furoate

- **The furoate ester group improves the pharmacokinetic properties of the drug. As a prodrug, it should be hydrolyzed into the free diloxanide to impart the amebicidal effect.**
- **It is used for the treatment of non-invasive intestinal amebiasis and asymptomatic carriers of *E. histolytica*.**

3) 8-Hydroxyquinolines



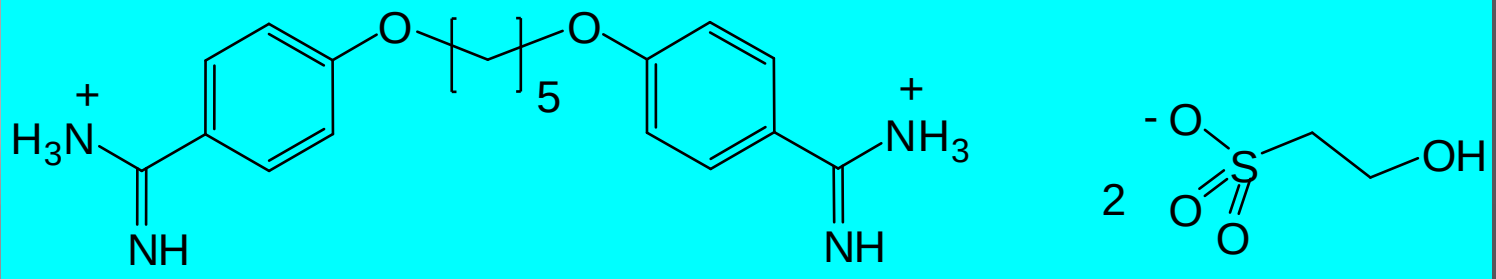
Oxine R=R'=H
Diodohydroxyquin, Iodoquinol R=R'=I

- **They are used in treatment of intestinal amebiasis.**
- **The main side effect of these agents is neuropathy.**
- **Their mechanism of action involves chelation of essential metal ions (m).**
- **Iodo groups (R and R') increase potency.**

B- Trypanosomicidal Drugs

- **Trypanosomiasis, sleeping sickness, in humans is of two types:**
  - **African trypanosomiasis, caused by *Trypanosoma gambiense* and *T. rhodesiense* and *T. congolense;***
  - **South American sleeping sickness (Chagas' disease) caused by *T. cruzi*.**

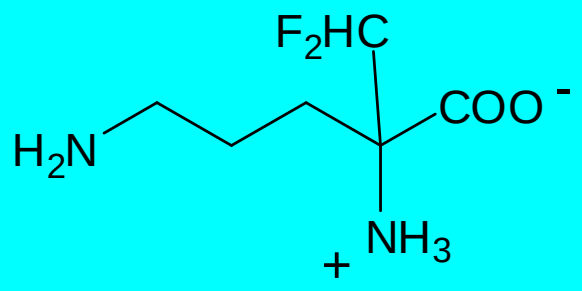
Pentamidine Isethionate



4,4'-[pentane- 1,5-diylbis(oxy)]dibenzenecarboximidamide

- **It is used for the prophylaxis and treatment of African trypanosomiasis.**
- **It is stored in the tissues for a long time so it is useful as a prophylactic agent.**

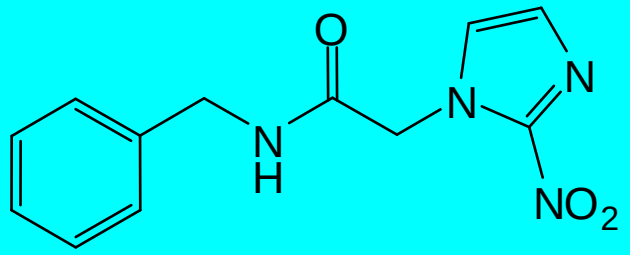
Eflornithine



DL-a-Difluoromethylornithine

- **It is used for treatment of *T. gambiense*. It is indicated in the meningo-encephalytic stage of the disease.**
- **It acts by inhibiting ornithine decarboxylase, a pyridoxal phosphate-requiring enzyme essential in DNA synthesis and cell proliferation.**

Benznidazole



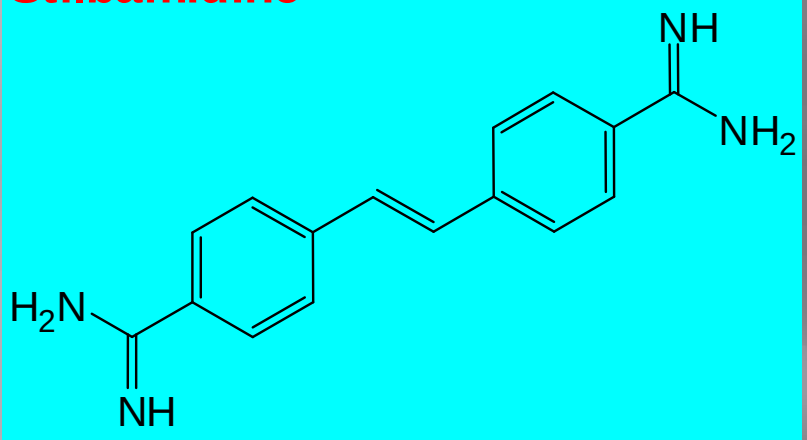
N-benzyl-2-nitroimidazole-1-acetamide

- **It is used in the treatment of Chagas' disease.**

C- Antileishmanial Drugs

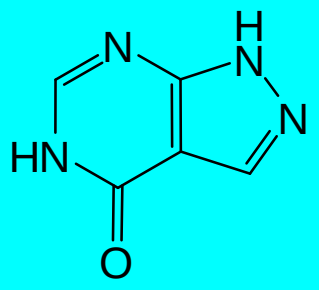
- **Leishmaniasis is a chronic tropical disease caused by *Leishmania donovani*. There are two types of leishmaniasis:**
  - **Visceral leishmaniasis, involving organs such as liver and spleen,**
  - **Cutaneous leishmaniasis characterized by slow-healing superficial ulcers.**
- **Antileishmanial drugs include:**
  - **Pentamidine isethionate,**
  - **Metronidazole,**
  - **Amphotericin B,**
  - **Stilbamidine and**
  - **Allopurinol.**

Stilbamidine



4,4'-Diamidinostilbene dihydrochloride

Allopurinol



1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one

Stilbamidine is structurally related to and is as effective as pentamidine.

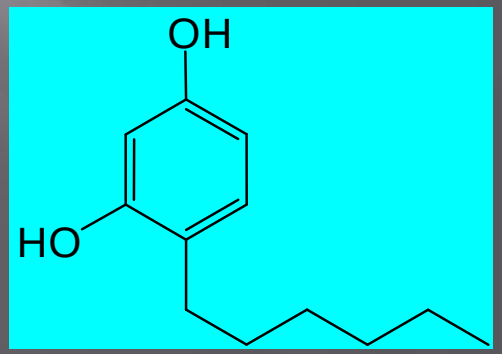
Allopurinol is used in treatment of gout and has recently been employed in the treatment of leishmaniasis.

D- Anthelmintic Drugs

- They are drugs used to eliminate parasitic worms from the body.
- They are classified according to their therapeutic use into:
  a. Drugs active against nematodes (pinworms, filarial worms,…etc.)
  b. Drugs active against cestodes (tapeworms)
  c. Drugs active against trematodes (bilharzial worms)

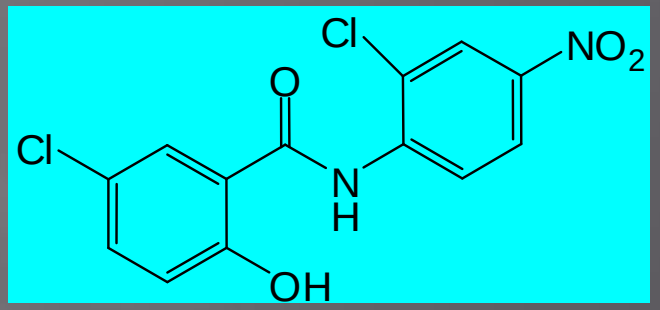
1. Hexylresorcinol

4-Hexylbenzene-1,3-diol



It is used in the treatment of mixed worm infections.
It is also used as antiseptic.

2. Niclosamide



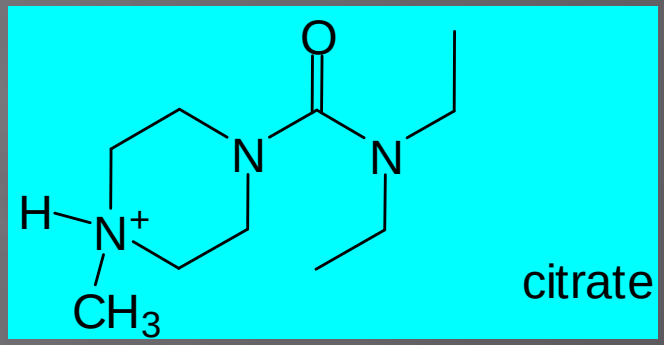
5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide

It is used against tapeworms.

Mode of action:

- **It interferes with the respiration of the worm, inhibits glucose uptake and protein synthesis.**
- **It inhibits the formation of trypsin inhibitor therefore it will facilitate the proteolytic action of the host digestive enzymes on the tapeworm.**

3. Diethyl carbamazine citrate



4-(diethylcarbamoyl)-1-methylpiperazin-1-ium citrate

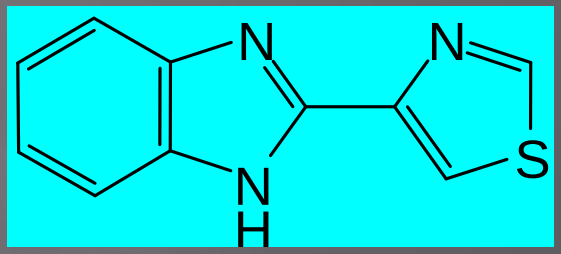
- **It is used in the treatment of ascariasis and filariasis.**

Mode of action:

- **It causes flacid paralysis of the worm (blocks neuromuscular junction).**

4- Thiabendazole

4-(1H-1,3-benzodiazol-2-yl)-1,3-thiazole

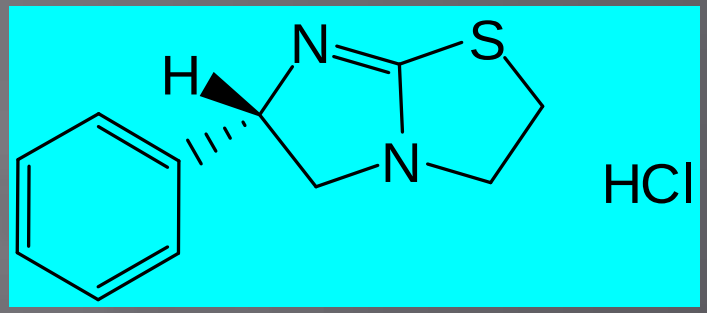


It is a broad spectrum anthelmentic drug effective against most of GIT helminths.

Mode of action:

- **It interferes with energy production in the worms through inhibition of fumarate reductase enzyme.**
- **It prevents glucose uptake by the worm.**

5- Levamisole



(S)-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole HCl

It is the levo isomer which is highly potent.

It is active against nematodes.

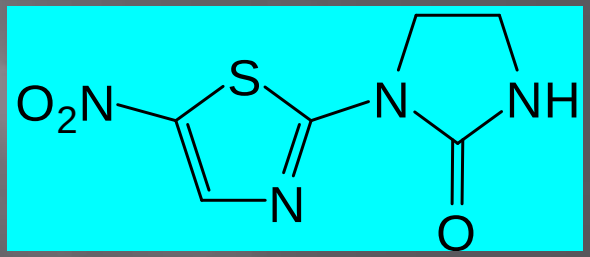
Mode of action:

It causes spastic paralysis in worms.

E- Antibilharzial Drugs

Schistosoma haematobium **(urinary)**
Schistosoma mansoni **(intestinal)**
Schistosoma japonicum **(liver and spleen)**

1. Niridazole

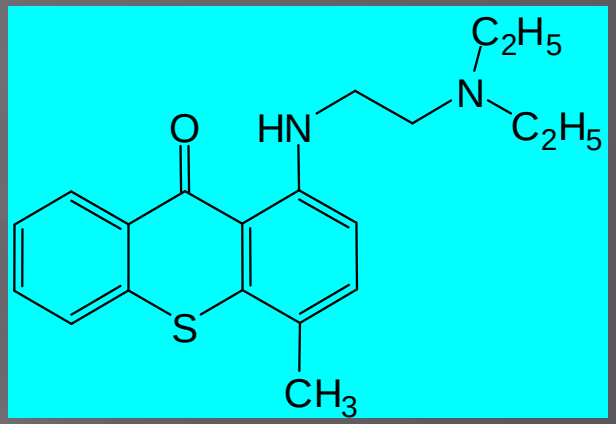


1-(5-nitro-1,3-thiazol-2-yl)imidazolidin-2-one

Mode of action:

It accumulates in the parasite causing inhibition of oogenesis and spermatogenesis.

2. Lucanthone

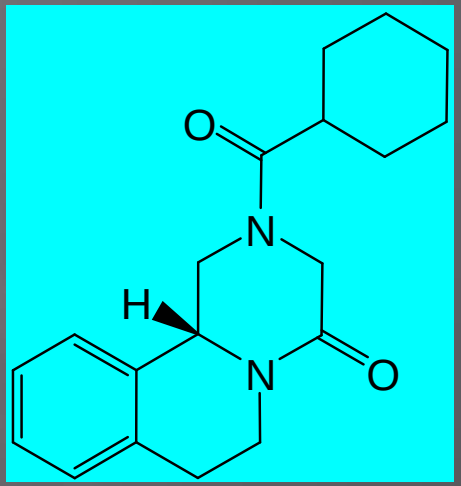


1-(2-(diethylamino)ethylamino)-4-methyl-9H-thioxanthen-9-one

It is active against the adult forms of bilharzial worms.
It is first converted to the active metabolite hycanthone (the 4-hydroxymethyl analog $CH_3 \rightarrow CH_2OH$).

3- Praziquantel

(*RS*)-2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one



It is active against cestodes and trematodes not nematodes.

Mode of action:

It increases cell membrane permeability leading to loss of intracellular calcium. This leads to paralysis of the worm.